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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/578,900	**Applicant(s)** CARULLI ET AL.	
	Examiner Jon Eric Angell	**Art Unit** 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 15 February 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,2,6,7 and 48-67*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). 7/14/04
13. ☐ Other: _____.

JON ANGELL
PATENT EXAMINER

Continuation of 3. NOTE: The proposed amendment to claim 6 would add a new step to the method which was not previously present in the claim and, therefore, would require new search and considerations. MPEP 714.13 states that Applicants cannot, as a matter of right, amend any finally rejected claims, except when an amendment merely cancels claims, adopts examiner suggestions, removes issues for appeal, or in some way requires only cursory review by the examiner. In the instant case, the proposed amendment to claim 6 requires more than a "cursory review". Therefore, the present amendment will not be entered

Continuation of 11. does NOT place the application in condition for allowance because: (see attached)

Continuation of 11. does NOT place the application in condition for allowance because:

Applicants assertion that the final rejection is improper because the presented arguments are incomplete in view of Applicants' amendment to the claims and introduction of new claims is not persuasive. Applicants contend that rejecting the claims for the reasons of record is improper because the rejection of record and the Office's response to Applicants arguments did not mention the amendments to the claims or the new claims. This is not persuasive because the amendmend claims and the new claims were still properly rejected under 35 USC 101 and 112, first paragraph for the reasons set forth in the 2/24/2005 Office Action as the amendments and new claims (which are dependent claims) do not overcome the utlity, and enablement issues indicated in the 2/24/2005 Office Action. Furthermore, Applicants arguments submitted 2/24/2005 did specifically indicate why the new claims, which are dependent claims, overcome the rejections of record. Accordingly, the Office's response in the Final rejection (11/15/2005) does not address arguments which are not present in the Applicants communication filed 8/23/2005. Applicants contend that in response to the arguments for the enablement rejection, the Office states that part of the rejection of the claims has been overcome and assert that this renders the rejection status of the claims is incomplete. In response, it is pointed out that page 9, second paragraph of the 11/15/05 Final Action indicated that with respect to the rejection of claims under 35 USC 112, 1st paragraph, the claims were amended rendering the rejection moot as it pertains only to an agent that inhibits the binding of a ligand to HBM and/or Zmax1. The 11/15/05 Action also clearly indicated that the amendment did not overcome the 112, 1st paragrpah rejection as a whole and specifically addressed the reasons why. This clearly indicated that the amendment only addresses one particular aspect of the rejection (i.e., the agents that inhibit the binding of a ligand to HBM and/or Zmax1) but does not overcome the rejection under 35 USC 112, first paragraph as a whole. Therefore, Applicants argument that the status of the claims is incomplete is not persuasive because the action clearly and correctly indicated that all claims were rejected under 35 USC 101 and 112, first paragraph. The applicants also argue that at no time does the Office specifically address why the new claims were rejected and assert that it is unclear how the prior Office Action can serve as a complete statement. In response, the prior statement is a complete statement because it sets forth the Office's reasons for rejecting all of the indicated claims as the amendment and new dependent claims were insufficient to overcome the rejection. Applicants also refer to M.P.E.P 707.07(d) with respect to the omnibus rejection of claims. In response, it is pointed out that M.P.E.P. 707.07(d) states, "A plurality of claims should never be grouped together in a common rejection, unless that rejection is equally applicable to all claims in the group." In the instant case the rejection of record is equally applicable to all claims in the group and, as such, the rejection is not an omnibus rejection. Therefore, Applicants request for withdrawal of finality is not persuasive because the claims were properly rejected for the reasons set forth in the Office Action dated

2/24/2005 as the amendments and new claims did not overcome the ultility and enablement rejections of record.

Applicants indicate that they have not received an acknowledged PTO form 1449 for the IDS submitted 7/14/2004. In response a copy of the acknowledged 1449 is included with this communication.

With respect to the rejection of claims under 35 USC 112, second paragraph, Applicants argue that the amendment to claims 6 and 7 obviate the rejection. In response, it is acknowledged that the amendment would overcome the rejection; however, the amendment has not been entered because it would raise new search and consideration issues. Since the amendment has not been entered, Applicants arguments are not persuasive.

With respect to the rejection of claims under 35 USC 101/112, first paragraph, Applicants argue that it is unclear how the claims can be rejected for the reasons of record (see 6.2 on page 8). In response, the claims are rejected for the reasons of record because the rejection set forth in the 2/24/2005 Office Action sets forth the proper basis for rejecting all of the claims including the amended claims and the new claims. That is, the amendment and new claims are properly rejected under 35 USC 112, first paragraph (enablement) for the reasons set forth in the 2/24/2005 Office Action. Applicants also argue that the office does not rebut that HBM is an allelic variant of Zmax1 or the argument that the nucleic acid encoding HBM and Zmax 1 are not from separate genes involed in separate signaling cascades. Applicants also argue that the specificaiton asserts a function for Zmax1 and HBM and state that, for example, Zmax1 and HBM are involved in bone modulation and assert that HBM expression in humans is correlated to an altered lipid profile and there is substantial support for this in the literature (see 6.2.1). In response, it is acknowledged that the Final Office action did not rebut that HBM is an allelic variant of Zmax1 or the argument that the nucleic acid encoding HBM and Zmax 1 are not from separate genes involed in separate signaling cascades because the assertion was accepted; however, it is pointed out that simply because one is the allelic variant of the other does not demonstrate that both have the same function. Furthermore, the assertion that the Zmax1 and HBM are "involved" in bone modulation does not impart a specific and substantial utility for HBM and Zmax1 because the mere observation that Zmax1 and/or HBM is "involved" in bone modulation does not indicate "how" they involved in bone modulation. Thus, additional experimentation would clearly be required in order to determine how HBM and Zmax1 are involved in bone modulation and lipid modulation. Additionally, the literature of record has been fully considered, and it is acknowledged that the post-filing literature supports Applicants' assertion that Zmax1 (LRP-5) may be involved in lipid regulation. However, merely observing that Zmax1 may be involved in lipid regulation does not establish a specific and substantial utility for Zmax1, and it does not establish utlity for HBM, which is a variant of Zmax1.

With respect to the Fujino 2003 reference, Applicants argue that the title alone, which reads "Low-density lipoprotein receptor-related protein 5 (LRP5) is essential for normal cholesterol metabolism and glucose-induced insulin secretion" ascribes a function to LRP5. Applicants argue that Fujino lays out that LRP5 can bind ApoE and refer to Fujino statements that "LRP5 is a multifunctional receptor involved in multiple pathways, including bone development, cholesterol metabolism, and the modulation of glucose-induced insuling secretion" and "LRP5 is required for proper hepatic clearance of chylomicron remnants and for glucose induced insulin secretion from the pancreatic islets, in addition to bone and eye development" as ascribing a function for LRP5/Zmax1. In response, the indicated teachings of Fujino's do not demonstrate a specific and substantial utility for Zmax1 because Fujino merely makes the observation that LRP5 is involved in, and required for, a specific type of lipid regulation (hepatic clearance of chylomicron remnants). Fujino does not teach, nor would it be readily apparent to one of ordinary skill in the art, how LRP5/Zmax1 is involved in cholesterol catabolism, including chylomicron clearance, without performing additional experimentation. Furthermore, it is pointed out that the instant specification does not appear to recognize or assert that Zmax1 is involved in hepatic clearance of chylomicrons. Additionally, Fujino does not specifically asociate the HBM variant of Zmax1 with lipid regulation whatsoever.

With respect to the Magoori reference, Applicants refer to Magoori's statement that, "LRP5 modulates the plasma clearance of diet-derived triglycerides in the absence of apoE by stimulating the hydrolysis of triglycerides" in support of their argument that Magoori provides a specific and substantial utility to the claimed invention. In response, it is pointed out that Applicants have paraphrased Magoori's statement. Without paraphrasing, Magoori states, "These observations suggest that LRP5 modulates the plasma clearance of diet-derived triglycerides in the absence of apoE by stimulating the hydrolysis of triglycerides." Therefore, Magoori merely makes the observation that LRP5 is involved in lipid regulation and does not teach how LRP5 functions in lipid metabolism. Rather, Magoori theorizes a potential function for LRP5 which would clearly require further experimentation to determine the validity of Magoori's theory. Furthermore, it is pointed out that the instant specification does not appear to recognize or assert that Zmax1/LRP5 modulates the plasma clearance of diet-derived triglycerides in the absence of apoE by stimulating the hydrolysis of triglycerides. Additionally, Magoori does not specifically asociate the HBM variant of Zmax1 with lipid regulation whatsoever.

Applicants also argue that Magoori supports the contention that modulation of a lipid through the LRP5 mechanism and screening models have a well-established utility. In response, Magoori contemplates that the specific double knock-out mouse that has a disruption of both the LRP5 gene and the ApoE gene and which has extreme hypercholesterolemia and advanced arthrosclerosis will provide a a useful animal model for research and development of therapeutic agents against extreme hypercholesterolemia and advanced arthrosclerosis. Accordingly,

Magoori only contemplates that the specific double knock-out mouse would be useful as an animal model for research purposes. Magorri does not contemplate or establish a well-recognized utility for the instant claimed methods.

With respect to the Office's position the additional experimentation would be required in order to determine a "real world" use for the identified reagent, Applicants argue that modulation of lipids such as HDL, VDL, cholesterol, or apoE via Zmax1 or HBM is a specific and substantial utility because an entire industry of lipid regulating drugs has evolved. This is not persuasive because even assuming, for arguments sake only, that the claimed methods of identifying reagents that merely bind to HBM, Zmax1 or the nucleic acids encoding HBM or Zmax1 could be used identify a reagent that may be involved in lipid regulation, additional experimentation would be required in order to determine the specific lipid or lipids that the reagent affects and to determine what specific effect the reagent has on the lipid(s) (e.g., increased lipid metabolism, decreased lipid metabolism, etc.).

With respect to Applicants arguments set forth on page 7, second full paragraph, Applicants argue that there is a real world use for screening reagents that modulate a lipid in an animal as indicated by Magoori and whether further experimentation may or may not be required for the identified drug for purposes of obtaining FDA approval or characterization of the reagent is not pertinent to the issue of whether the claimed method of identifying reagents has a utility. In response, it is pointed out that the proposed amendment has not been entered. Accordingly, pending claims 6, 7 and 67 do not explicitly indicate that the method includes administering the reagent to a cell to determine modulation of a lipid in a cell. Furthermore, Magoori does not demonstrate a real-world (i.e., well-established) utility for the instant claimed methods as indicated above. Additionally, the issue is not whether or not further experimentation would be required for FDA approval, the issue is that further experimentation is required to establish patentable utility for the claimed methods. For example, additional experimentation is required to determine the specific lipid or lipids that the reagent affects, to determine what specific effect the reagent has on the lipid(s), etc. As indicated in the 11/15/2005 Final Office Action, utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities (MPEP 2107.01). Applicants are also reminded that MPEP 2107.01(c) indicates that a method of assaying for or identifying a material that itself has no specific and/or substantial utility does not constitute a substantial utility.

With respect to Applicants argument that claims 66 and 67 both list triglyceride and VLDL as the lipids which are modulated and that the argument should respectfully be withdrawn, it is acknowledged that claims 66 and 67 indicate that either triglyceride and/or VLDL are modulated. Accordingly, the assertion that all of the claims are directed to any lipid is respectfully withdrawn. However, the indication that the lipid that is modulated is either triglyceride and/or VLDL does not establish a nexus between identifying a reagent that binds to HBM or Zmax1 (or a nucleic acid

encoding HBM/Zmax1) and the modulation of the triglyceride/VLDL because further experimentation would be required to determine if the mere binding of the reagent to HBM/Zmax1 (and a nucleic acid encoding HBM/Zmax1) actually caused the modulation of a lipid molecule (including triglyceride and VLDL).

Applicants argue that M.P.E.P. § 2107.01(C) states that "[m]any research tools such as... screening assays... have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds)." Applicants assert that this is the case here where the instant invention is a research tool for analyzing compounds that bind to HBM and/or Zmax1 and have lipid modulating activity and, therefore, the claims should have utility.

In response, M.P.E.P. § 2107.01B states, "the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use and, therefore, do not define 'substantial utilities'... (c) A method of assaying for or identifying a material that itself has no specific and/or substantial utility". In the instant case, as previously indicated, the claims are drawn to a method of assaying for or identifying a molecule that itself has no specific utility. Therefore, the instant claims do not have substantial utility per M.P.E.P. § 2107.01B. Furthermore, considering M.P.E.P. § 2107.01B as indicated above, the indication in M.P.E.P. § 2107.01(C) that screening assays (in general) have clear, specific, and unquestionable utility can only be applicable in situations where the identified material itself has a specific and/or substantial utility. Since this is not the case here, Applicants arguments are not persuasive.

Applicants assertion that the Office's assertion on page 8 regarding what "modulates" encompasses is not pertinent the utility rejection. In response, the Office was merely indicating that "modulates" is interpreted very broadly, given the absence of any specific definition. Furthermore, the breadth of the term "modulates" is pertinent to the utility rejection because identification of a reagent that merely "modulates" lipid regulation does not impart a specific utility to the reagent because further experimentation would be required to determine what modulating affect the reagent has on lipid regulation.

With respect to the rejection of claims under 35 USC 112, first paragraph that one of skill in the art would not know how to use the claimed invention based on the lack of support of a specific and substantial utility or a well-established utility for the reasons of record set forth in the 2/24/05 Office Action, Applicants argue that it is unclear how the claims can be rejected for the reasons of record when claims have been amended and new claims have been added. In response, the claims are rejected for the reasons of record because the rejection set forth in the 2/24/2005 Office Action sets forth the proper basis for rejecting all of the claims including the amended claims and the new claims. That is, the amendment and new claims are properly rejected for the reasons set forth in the 2/24/2005 Office Action. Applicants also argue that there is no portion of the "Response to Arguments" on pages 4 to 9 which are specifically directed to

the 112, first paragraph - enablement portion of the combined rejection and assert that a prima facie case of lack of enablement has not been adduced by the Office for the claims as currently pending. In response, since the claimed invention does not have patentable utility (as previously indicated and reiterated herein) one of skill in the art would clearly not know how to use the claimed invention. Accordingly, the claims are properly rejected under 35 USC 101 and 112, first paragraph for the reasons indicated in the utility rejection. Applicants arguments pertaining to the utility rejection (which are also applicable to the enablement rejection where it is based on the utility rejection) are addressed in the Final Office Action on pages 4-9. It is pointed out that should the claims be determined to have patentable utility the rejection the combined rejection of claims under 35 USC 101 and 112, first paragraph (i.e., the rejection set forth on pages 4-9 of the 2/24/05 Action) would be withdrawn. However, it is pointed out that the claims are also rejected under 35 USC 112, first paragraph (enablement) separate from the utility rejection for the reasons set forth on pages 12-18 of the 2/24/05 Action. It is noted that withdrawal of the utility rejection would NOT necessitate withdrawal of the 112, first paragraph (enablement) rejection set forth on pages 12-18 of the 2/24/05 Office Action.

With respect to Applicants concern about the issue of equity, fairness and patent term adjustment (see pages 12-14), Applicants are reminded that the apropriate time to request patent term adjustment is after a notice of allowability has been issued.

With respect to the rejection of claims under 35 USC 112, first paragraph, Applicants argue that it is unclear how the rejection can be maintained for the reasons of record in view of the amendments and the new claims. In response, the claims are rejected for the reasons of record because the rejection set forth in the 2/24/2005 Office Action sets forth the proper basis for rejecting all of the claims including the amended claims and the new claims. That is, the amendment and new claims are properly rejected for the reasons set forth in the 2/24/2005 Office Action.

Applicants also contend that (1) the statement posited on page 9 of the "Response to Arguments" conflicts with the status of the rejection set forth on pages 3-4, and (2) there seems to be a change of rejection status indicated for the rejection on page 9.

In response, it is pointed out that page 9, second paragraph of the 11/15/05 Final Action indicated that with respect to the rejection of claims under 35 USC 112, 1st paragraph, the claims were amended rendering the rejection moot as it pertains only to an agent that inhibits the binding of a ligand to HBM and/or Zmax1 and not to the the 112, 1st paragrpah rejection as a whole. This clearly indicates that the amendment only addresses one particular aspect of the rejection (identifying an agent that inhibits the binding of ligand to HRM and/or Zmax1) but does not overcome the rejection under 35 USC 112, first paragraph as a whole. Therefore, the statement on page 9 does not conflict with with the status of the rejection set forth on pages 3-4 and the

only change in the rejection is as it pertains only to an agent that inhibits the binding of a ligand to HBM and/or Zmax1, and not the entire rejection. Accordingly, all claims are properly indicates as being rejected under 35 USC 112, first paragraph (enablement) for the reasons previously set forth and the status of the rejected claims is clear.

With respect to the Office's position that lipid modulation is a complex process that can be influenced by a number of different factors based in part on the teachings of Ye et al., Applicants reiterate their argument presented in the Appeal Brief filed 7/2/04. Specifically, Applicants argued that:

> ... Ye et al reviews a series of polymorphisms in various genes involved in lipid regulation. ....Ye et al. reports that studies of the effects of dietary cholesterol have not been consistent due to a series of confounding factors. This only means that it remains to be determined under what circumstances and for which polymorphisms dietary intervention is indicated. However, Ye et al. does not in any way cast doubt on whether those polymorphisms, or the HBM polymorphism, appear in genes related to lipid regulation. Ye et al only shows that diet alone may not have a consistent effect. It cedainly does not provide a reason to doubt the utility of the present invention. The question of whether a dietary change can affect lipid profiles simply has no bearing on the question of whether identifying a molecule that binds to a protein involved in lipid regulation (such as HBM or Zmaxl) has credible utility as a method for identifying a molecule that is involved in lipid regulation.

In response, Ye et al. teaches that lipid regulation is a complex multi-factorial process that involves a number of different factors including diet as well as genetics, and specifically indicates a number of different genes and polymorphisms that are involved in lipid regulation. Ye et al. is pertinent to the instant case because it establishes that many different factors can be involved in lipid regulation. In view of the complex nature of lipid regulation, as taught by Ye et al., it is clear that a mere observation that a gene or polymomhism (such as HBM or Zmaxl) is associated with a particular lipid level does not establish that the gene or polymophism is directly involved in lipid regulation. Furthermore, LDL receptors were recognized in the prior art to be a family of receptors that may be involved in lipid regulation, but may also have functions that are not related to lipid regulation (e.g., Willnow et al.). Therefore, in view of the totality of the prior art, it is clear that a mere observation that HBM and Zmax1 are associated with lipid regulation and that they are members of the LDL receptor family of proteins is not sufficient to establish that HBM and Zmaxl are directly involved in lipid regulation and additional experimentation would be required to establish that the gene or polymorphism is actually directly involved in lipid regulation.

Applicants argue that claims have been amended and new claims have been introduced. In response, it is pointed out that the amendment filed 2/15/2006 has not been entered for the reasons indicated herein and that no new claims were presented in the 2/15/2006 amendment.

Applicants argue that methods of screening for changes in lipid patterns were well known in the art at the time of filing and specifically refers to the teachings of Kita et al., Magoori et al., and Lafont et al. Applicants contend that the complexity of lipid metabolism and the interaction of many genes does not off set the tools that were available for screening changes in lipid pattern and the ability to detect these changes. In response, it is acknowledged, and the Office does not contest, that methods of screening for changes in lipid patterns were known in the art. However, simply being able to screen for changes in lipid metabolism does not provide an enabling disclosure for the claimed invention which because determining changes in lipid patterns does not enable a method for using HBM, Zmax1, a nucleic acid encoding HBM or a nucleic acid encoding Zmax1 for identifying a reagent that modulates a lipid. Additional experimentation would be required to determine HBM and Zmax1 involvement in lipid regulation.

Applicants disagree with the Office's position that there is no disclosure in the specification which indicates that HBM and Zmax1 are functional LDL receptors that are directly involved in lipid modulation. Applicants assert that (1) Zmax1 binds to apoE, (2) individuals expressing HBM have a different lipid profile than those expressing the wild-type type gene, and (3) the specification states that HBM and Zmax1 are involved in lipid regulation. Applicants contend that these facts/assertions coupled with at least the facts of Magoori et al. and Fujino et al., which (Applicants assert) show that LRP5 is directly involved in apoE regulation provide evidence that HBM and Zmax1 are involved in lipid regulation.

In response, Applicants arguments have been fuly considered but are not peruasive because Zmax1 binding to apoE, asssociation of HBM expression with an altered lipid profile, and the mere statement that HBM and Zmax1 are involved in lipid regulation merely associate HBM and/or Zmax1 with lipid regulation and does not establish that the claimed method is fully enabled for identifying reagents that modulate a lipid, especially in view of the art of record which indicate that modulating a lipid is a complex process that involves the action of many different genes as well as other factors such as diet (e.g., Ye et al.), and that LDL receptors can be invovled in functions other than lipid modulation (e.g., Willnow et al.). Even in view of the post filing art (Magoori et al, and Fujino et al.), Zmax1 and HBM were not shown to be anything more than associated with lipid regulation at the tmie of filing. Therefore, based on the state of the art at the time of filing, and an undue amount of additional experimentation was required to determine if and how HBM and Zmax1 are functionally involved in lipid regulation.

Applicants disagree with the Office's conclusion that additional experimentation would be required in order to fully enable the claimed methods in view of the fact that lipid regulation is a complex multifactorial process and the fact that HBM and Zmax1 may be involved in pathways unrelated to lipid modulation. Applicants assert that the Fujino reference, which was reviewed by Nobel laureate recipients in the field of lipid regulation, states that LRP5 is a multifunctional receptor involved in multiple pathways including bone development, cholesterol metabolism, and

the modulation of glucose-induced insulin secretion. Applicants contend that the multifunctional nature of the pathway is accepted by those artisans practicing in the field and it should likewise be accepted by the Office. Applicants also conetnd that the multifunctional nature of the pathway does not negate LRP5/Zmax1's or HBM's involvement in modulation of a lipid.

In response, it is acknowledged that the Fujino reference was reviewed by Noble laureate recipients and that Fujino states that their data indicate that LRP5 is a multifunctional receptor involved in multiple pathways including bone development, cholesterol metabolism, and the modulation of glucose-induced insulin secretion. However, it is respectfully pointed out that recognizing that LRP5 is involved in multiple pathways does not establish that the instant claimed invention was fully enabled at the time of filing for identifying reagents that modulate lipid regulation the mere involvement of LRP5 does not establish what functional role LRP5 has in the multiple pathways. Furthermore, the teaching that that LRP5 is involved in mutliple pathways supports the Office's position that additional experimentation would be required because the mere binding of a reagent to Zmax1/HBM would not be indicative as to which, if any, of the multiple pathways the reagent would affect. Addtionally, the observation that LRP5/Zmax1 is involved in lipid regulation does not necessarily mean that HBM is also involved in lipid regulation as Zmax1 and HBM are structurally and functionally different molecules, as evidenced by the instant specification which discloses that HBM but not the wild-type Zmax1 is associated with and involved in high bone mass.

With respect to the Magoori et al and Fujino et al. references, the Applicants indicate that they do not concede that Magoori and Fujino do not disclose how LRP5 is involved in lipid regulation. Applicants contend that both references discuss LRP5 involvement in regulation of a lipid, and assert that Fujino discusses that LRP5 directly and indirectly modulates apoE.

In response, it is the Office's position that neither Magoori or Fujino disclose how LRP5/Zmax1 or HBM is specifically involved in lipid regulation Fujino and Magoori merely make the observations that LRP5 is involved in specific type of lipid regulation neither of which were specifically contemplated by the specification. Furthermore, Fujino and Magoori do not teach, nor would it be readily apparent to one of ordinary skill in the art, how LRP5/Zmax1 is involved in the lipid regulation without performing additional experimentation. Additionally, neither Fujino nor Magoori teach that the HBM variant is involved in lipid regulation.

Therefore, Applicants arguments are not persuasive.

JON ANGELL
PATENT EXAMINER